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APPLICANTS:	Mueller-Walz et al.	CONFIRMATION NO.:	2553
SERIAL NUMBER:	10/575,656	EXAMINER:	KENNEDY, N.
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FOR:	DRY POWDER FORMULATIONS		

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection of the claims mailed November 22, 2010. A response was filed February 22, 2011. An Advisory Action was mailed March 9, 2011 indicating that the response was entered and considered but that the rejection of the claims under 35 U.S.C. § 103(a) was maintained. This request is being filed along with authorization for payment of the fee for a one-month extension of time. With a one month extension of time, a paper filed on or before March 22, 2011 is considered timely. A Notice of Appeal is being filed concurrently with this paper.

The claimed invention relates to dry powder formulations for use in a dry powder inhaler (DPI). The use of magnesium stearate to improve the flowability of DPI powders was known in the art. Applicants' specification characterizes the prior art as teaching "that any beneficial properties that derive from the use of magnesium stearate [in DPI formulations] are predicated on its apparent ability to alter the surface properties of carrier particles" and that "as high a surface coating should be obtained with as little magnesium stearate as possible." Specification at p. 3, lines 27-30. The specification further teaches that the small amounts (less than 0.5%) of magnesium stearate believed to be tolerable in DPI formulations were generally too low to take advantage of the ability of magnesium stearate to stabilize against moisture (both atmospheric humidity and the hygroscopic effects of some active agents.) Specification at p. 4, line 6 to p. 5 line 2; at p. 3, lines 1-4 *citing* Staniforth *et al.*, *J. Pharm. Pharmacol.* 34:141-145 (1982) (C5 of IDS filed 9/29/10) for its teaching that magnesium stearate in amounts of 0.5% to 4% destabilizes the powder causing significant segregation; and at p. 3, lines 6-21, citing U.S. Patent No. 6, 528, 096 for its description of the lubricant properties of magnesium stearate and its

teaching that magnesium stearate should be used in amounts of less than 0.5% to achieve a surface coating of the carrier particles of over 10%.

The present invention is based upon Applicants' discovery that the effect of surface coverage of magnesium stearate on the performance of dry powders is minor compared to its moisture protection and lubricating properties. Specification at p. 5, lines 4-12. Thus, Applicants discovered that a powder having a reproducibly high fine particle fraction (FPF) could be achieved using higher amounts of magnesium stearate (at least 0.5% by weight of the formulation) than the amounts believed to be advantageous in the prior art, provided that the surface coverage of the carrier particles by magnesium stearate was kept low (less than 5%), as evidenced by Examples 1-5 of Applicants' specification.

Claim 1 is directed to a dry powder formulation for inhalation, comprising active particles and carrier particles for supporting the active particles, the formulation further comprising magnesium stearate in an amount of at least 0.5% by weight of the formulation, wherein the particles of magnesium stearate are disposed on the surface of the carrier particles to provide a surface coverage of less than 5% on the carrier particles (emphasis added). The remaining claims depend, either directly or indirectly, from claim 1.

The rejections under 35 USC § 103(a) of claim 1 and its dependent claims as unpatentable over WO 01/078693 ("Staniforth") in view of U.S. 6,521,260 (also by Staniforth, assigned to Vectura Ltd., "Vectura") should be withdrawn because the combination of Staniforth and Vectura fails to establish a *prima facie* case of obviousness with respect to claim 1.

First, the combination of Staniforth and Vectura fails to describe or suggest a formulation comprising carrier particles wherein the coverage of the magnesium stearate on the surface of the carrier particles is less than 5%, as required by claim 1. Instead, Staniforth describes a surface coverage of the carrier particles that is "at least 5%, preferably at least 15%." Staniforth at p. 11, lines 5-8 (emphasis added). Vectura does not describe a surface coverage of the carrier particles that is less than 5%. Nevertheless, the Examiner contends that Vectura provides the motivation to try using less than 5% coverage with an expectation of the same result as Staniforth. Final Office action at p. 4-5, bridging paragraph. But Vectura unambiguously states that it is preferable to "saturate" the surface of the carrier particles with additive, meaning that "even if

more additive material were provided substantially the same covering would be achieved." Vectura at col. 7, lines 20-24. This is consistent with Staniforth's teaching that a higher coverage is desirable, notwithstanding that this coverage may be discontinuous. This is also consistent with the reference in Staniforth to WO 2000/53157 ("Chiesi") for its description of the use of magnesium stearate to partially coat the surface of carrier particles. Staniforth at p. 6, lines 19-23. Chiesi explicitly teaches that it is desirable to coat as much of the surface of the carrier particles as possible using a small amount of a "lubricant", which is preferably calcium stearate. Chiesi at p. 5 lines 6-9 and p. 6 lines 20-22. Specifically, Chiesi teaches that the coating should be more than 10% and preferably more than 35%. Chiesi at p. 6, lines 5-12.

To summarize, in view of (1) the express teaching in Staniforth that the surface coverage of the carrier particles is "at least 5%, preferably at least 15%" combined with (2) Staniforth's reliance on Chiesi for its description of the use of magnesium stearate to coat the carrier particles, and (3) Chiesi's explicit teaching that the coating should be more than 10%, preferably more than 35%, and (4) further in view of Vectura's explicit teaching that it is desirable to "saturate" the surface of the carrier particles, the skilled person would not have had a reasonable expectation of success in modifying Staniforth as suggested by the Examiner to arrive at a coverage of the magnesium stearate on the surface of the carrier particles that is less than 5%, as required by claim 1.

Second, the combination of Staniforth and Vectura fails to provide a reasonable expectation of success in making a DPI powder formulation comprising at least 0.5% by weight of magnesium stearate, as required by claim 1. The skilled person would have lacked a reasonable expectation of success based on the mere recitation in Staniforth (at p. 14, lines 12-17) of the broad range of from 0.02% to 1.5% magnesium stearate because it was commonly understood that only small amounts of additive and "particularly small amounts" of magnesium stearate as additive should be used to coat carrier particles for DPI powders. *See e.g.*, Vectura at col. 3, lines 56-60. Indeed, Vectura expressly teaches away from using magnesium stearate as an additive in an amount of 1.5% by weight (based upon the weight of the formulation), stating that this amount causes premature segregation of active particles from the carrier particles. Vectura col. 2 line 61 to col. 3 line 1. Thus, the high end of the range described by Staniforth is expressly

discredited by Vectura. Vectura does not specify the amount of magnesium stearate that can be used, nor does Vectura exemplify a dry powder formulation containing magnesium stearate. Vectura therefore fails to provide any reason for the skilled person to expect success over the entire broad range of magnesium stearate recited by Staniforth.

Staniforth itself also fails to provide an expectation of success for using at least 0.5% by weight of magnesium stearate, as required by Applicants' claims. Although Staniforth describes ranges that include the claimed range, the skilled person would not have expected success in using at least 0.5% magnesium stearate in view of the prior art teaching by Staniforth, discussed above, that the use of magnesium stearate within the range recited by Applicants' claims (*i.e.*, in amounts of 0.5% to 4%) destabilizes the powder formulation causing significant segregation of active particles from carrier particles. The skilled person having knowledge of Staniforth and Vectura would also have knowledge of Staniforth's earlier publication expressly teaching away from the claimed range. Moreover, Chiesi, which as noted above is relied upon by Staniforth for its description of the use of magnesium stearate to coat the carrier particles, explicitly directs that the amount of magnesium stearate should be less than 0.5%. *See* Chiesi *e.g.*, Abstract. Further, the Examples of Staniforth itself discourage the skilled person from using magnesium stearate in amounts of more than 0.5% because higher amounts are shown to reduce the fine particle fraction (FPF) of the powder (see Table 6 at p. 23 of Staniforth). And all subsequent examples utilize magnesium stearate in amounts less than 0.5% by weight of the formulation (*see e.g.*, Examples 7-12 of Staniforth). Accordingly, the skilled person would not have had a reasonable expectation of success in combining Staniforth and Vectura to arrive at a formulation comprising at least 0.5% by weight of magnesium stearate, as required by claim 1 because Staniforth itself (viewed in its entirety, that is with knowledge of Chiesi and the earlier Staniforth publication) would lead the skilled person to expect that amounts of magnesium stearate within this range would destabilize the powder formulation. And the combination of Staniforth and Vectura fails to provide any reason to overcome that expectation.

For the reasons stated above, the combination of Staniforth and Vectura fails to establish a *prima facie* case of obviousness with respect to claim 1, or its dependent claims. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 is requested.

Applicants submit that the application is in condition for allowance and request an action for same. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 50-0311, Reference No. **28069-625N01US**.

Respectfully submitted,

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